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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,527	12/05/2003	James A. Williams	D-2939CIPCONDIV3	3304

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,527	WILLIAMS, JAMES A.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/13/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-38 have been canceled. New claims 39-45 have been submitted

Amended Claims 25-37 have been submitted.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

1. The information disclosure statement filed June 13, 2005 has been considered.

2. ***Double Patenting (Maintained)*** The rejection of claims 39-41 and 44, as previously applied to claims 25-26, 29-33, and 35-37 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 10 of U.S. Patent No. 5,919,665 is traversed on the grounds that the claim amendments have obviated this rejection and if the rejection has not been overcome, will consider filing a Terminal Disclaimer upon the indication of allowable subject matter.

3. It is the position of the examiner that the rejection had not been obviated because an effective Terminal Disclaimer has not been received therefore the rejection is maintained.. Although the conflicting claims are not identical, they are not patentably distinct from each other because the allowed claims are directed to a species of invention of the instantly claimed genus of botulinum toxins; the allowed species anticipates the instantly claimed genus of botulinum toxins.

4. ***Claim Objections (Withdrawn)*** Claims 25, objected to because of informalities has been obviated through cancellation of the claims.

5. ***Claims Objection (Maintained)*** Claim 42 is objected to for the reasons set forth for prior claim 28 (page 3, subparagraph 2). Claim 42 should modify the composition of claim 39, --

wherein the composition is a solution--------, or ------ wherein the composition further comprises a solution-----.

1. **(Rejection Maintained)** The rejection of claims 39, 42 are rejected under 35 U.S.C. 102(e) as being anticipated by Dolly et al (US Pat. 6,203,794, effective filling date May 31, 1994) as evidenced by Ledoux et al (1994) as previously applied to claims 25-26,31-33, 35-37 is traversed on the grounds that the claims 25-26,31-33, 35-37 have been canceled and Dolly et al does not specifically disclose, teach or suggest the present invention directed to a soluble recombinant C-terminal botulinum toxin that comprises a non-toxin protein sequence and a receptor binding domain amino acid sequence of a botulinum toxin.

2. It is the position of the examiner new claims 39 and 42 still read on Dolly et al, because what is claimed is a product by process composition, and the product of Dolly et al comprised a C-terminal portion of the heavy chain of botulinum toxin A, though not produced recombinantly, is the same or equivalent product as the compositions of claims 39 and 42 are not structurally distinguished from compositions that comprise the C-terminal portion of botulinum toxin A produced by a different process. Additionally the composition of Dolly et al comprised a pharmaceutically acceptable solution excipient (see Dolly et al, col. 41, lines 66-67). The reference still anticipates the newly submitted claims directed to a different embodiment than what claims 25-38 had previously set forth.

3. Applicant asserts that compositions of Dolly et al comprise a recombinant light chain and uses MBP in the formation of the botulinum toxin and the present claims are directed to composition that comprise the C-terminal portion of a heavy chain of botulinum toxin.

4. It is the position of the examiner that Dolly et al's compositions comprise the C-terminal portion of a heavy chain (see Dolly et al col. 7, lines 32-35, that comprise the C-terminal fragment,(heavy chain targeting portion, Dolly et al, claim 4, and col. 5, lines 12-14) of botulinum toxin (see Dolly et al, col. 7, lines 18-30, and col. 41, claims 2-3). Applicant's compositions do not exclude the presence of additional botulinum

neurotoxin chains and therefore still read on the compositions disclosed in Dolly et al for reasons of record and responses set forth above.

New Grounds of Objection Necessitated by Amendment

Specification

8. The amendment filed June 10, 2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The changes in amino acid sequence for SEQ ID NO 24 and 32 through the addition of two amino acids to each sequence at the C-terminal, "Met Ala", introduces New Matter into the instant Specification as no original descriptive support could be found for the newly amended sequences. Applicant has not pointed out wherein the instant Specification support for theses changes can be found. Sequences cannot be changed unless specific support forth the sequence changes can be found in the Specification. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 102

5. New Claims 39-43 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by LaPenotiere et al (1993; presented in May 1992 International Conference on Botulinum, Tetanus Neurotoxins, reference cited on Applicant's USPTO 1449) in light of Ledoux et al (1994, reference of record) who teaches botulinum toxin to be a water soluble protein.

LaPenotiere et al disclose the instantly claimed invention directed to:
a recombinant (LaPenotier et al, "molecular engineered", title)

botulinum (see title) toxin (neurotoxin)

protein (Hc polypeptide fused to E.coli maltose binding protein, see LaPenotiere et al, abstract), wherein

the soluble C-terminal portion (in light of Ledoux et al who teaches botulinum toxin is inherently a water soluble protein) is

produced by a process using an aerobic bacteria (E.coli grows in the presence of oxygen, see E.coli expression, abstract),

the polypeptide being expressed as a single fusion protein polypeptide in a bacteria, that is free of neurotoxin complex proteins, as only the Hc portion was recombinantly expressed in E.coli, wherein the toxin is in a solution ("dilutions", see page 464, paragraph 3; "culture medium", and "resuspended" see page 464, paragraph 4; in complete Freund's (see page 465, paragraph 2). The C-terminal botulinum toxin recombinant protein of LaPenotiere et al inherently anticipates the instantly claimed invention.

1. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

2. Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states AArtisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art=s functioning, does not render the old composition patentably new to the discoverer. AThe Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the

prior art≅.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over LaPenotiere et al in view of Williams et al (US Pat. 5,601,823, reference cited on Applicant's US PTO-1449).

9. See discussion of LaPenotiere et al above. LaPenotiere et al teaches and produces a recombinant clostridium botulinum toxin C-terminal fragment protein that is expressed in an aerobic bacteria and is produced as a single polypeptide chain, wherein the single polypeptide chain comprises an additional maltose binding protein polypeptide sequence coupled to the C-terminal portion of the botulinum toxin but differs from the instantly claimed invention by failing to show the additional coupled polypeptide to be a polyhistidine tract.

10. Williams et al teaches the production of recombinantly produced clostridium (botulinum and difficile(see col. 3, lines 25-29)) toxins as single chain polypeptides (see col. 8, lines 13-22, lines 59-63) either through coupling the toxin to a maltose binding protein polypeptide or to a polyhistidine tract polypeptide (see col. 35, lines 26-49, Example 11) in an analogous art for the

purpose of producing large quantities of recombinant toxins for formulation of vaccines and generation of neutralizing antibodies induced to the recombinant clostridium toxins.

11. It would have been obvious to the person of ordinary skill at the time the invention was made to modify the recombinant polypeptide of LaPenotiere et al that comprised a maltose binding protein non-toxin protein with the polyhistidine tract of Williams et al because Williams et al teaches and shows the successful production of recombinant clostridium toxins and teaches prokaryotic expression systems for the attainment of recombinant Clostridial toxins through expression of single polypeptide chains, wherein the single polypeptide chains will bind to a ligand containing column to aid in protein isolation and purification, the polypeptides including either a maltose binding protein or a polyhistidine tract polypeptide tag (pET16b) (see Example 11, column 35), and these methods serve to define means for attainment of high levels of recombinant toxin.

12. The person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a botulinum C-terminal portion recombinant protein that comprises a polyhistidine tract utilizing the expression system of Williams et al because both LaPenotiere et al and Williams teach the utilization of maltose binding protein expression system for the recombinant expression of Clostridial toxins and Williams also successfully showed the recombinant expression of a Clostridial toxin using a polyhistidine tract polypeptide which provides the advantage of attaching the polypeptide polyhistidine tract either at the C-terminal end (pET23a-c) or the N-terminal end (pET16b) (see Example 11, col. 35, lines 26-49) of the Clostridial polypeptide depending on the preferred location of the non-toxin polyhistidine tract

polypeptide. In the absence of a showing of unexpected results, LePenotiere et al in view of Williams et al obviate the instantly claimed invention.

Conclusion

2. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
August 31, 2005

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